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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
SAKELARIS, SALLY A

ART UNIT	PAPER NUMBER
1634	11

DATE MAILED: 12/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,992	UITTERLINDEN ET AL.	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *1-16 and 20-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4 and 7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Arguments

Election/Restrictions

It is noted that claim 20 is an improper use claim. In the event that applicant intended claim 20 to be a product claim, it is currently, properly grouped in Group III with the other kit claims. In the event that applicant intended claim 20 to be a method claim, it should instead be included in the method claims of group I. Either way, groups I and III remain withdrawn from prosecution as being drawn to non-elected inventions pursuant to applicant's election of Group II.

Applicant's arguments filed 9/30/02 have been fully considered but they are not persuasive. Applicant's election with traverse of Group II, claims 17-19 in paper No. 10 is acknowledged. The traversal is on the ground(s) that Group I, Group II and Group III share the common inventive concept that a subject's susceptibility to heart disease, and treatment therefore, can be predicted by analyzing the subject's genetic material and determining whether specific restriction enzyme site polymorphisms are present or absent in the vitamin D receptor gene. Additionally, applicants argue that the foregoing common inventive concept, and special technical features, that link Groups I, II, and III, are a contribution over the teachings of Spector et al. because Spector et al. do not teach or suggest the existence of restriction enzyme site polymorphisms that are predictive of susceptibility to heart disease. However, Groups I, II, and III are still appropriately separated as lacking unity since the lack of unity still exists between the three groups. Applicant is reminded of the PCT practice of including a single product, single method of using, single method of making etc. in an application. The inventions listed as Groups

I-III do not relate to a single inventive concept under PCT Rule 13.1 because under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The technical feature of Group III appears to be the primers capable of amplifying a portion of the VDR gene.

However, Spector et al. (WO 97/40187) teach primers specific for amplifying the Vitamin D receptor gene. Since the technical features linking the inventions was known in the art, it does not provide a contribution over the art and does not constitute a "special technical feature." With respect to groups I and III of the present application, unity is correctly broken as the groups are directed to multiple, different methods ie, Group I, to a method of determining susceptibility to heart disease, and Group II, a method of predicting response of a subject to treatment. Accordingly, Groups I-III are not so linked by the same or a corresponding special technical feature as to form a single general inventive concept.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 17-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of predicting a human patient's response to at least 1302 mg/day of calcium treatment by assaying for the presence of the baT VDR haplotype wherein patients having the baT VDR haplotype are more likely to experience increased risk of myocardial infarction and cardiac arrythmias in response to calcium treatment, does not reasonably provide for methods which predict any patient's response to any treatment in any

amount by assaying for any B/b, A/a, T/t VDR haplotype nor does it enable the administration of any treatment in any amount. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 17-19 are broadly drawn to methods for predicting any patient's response to any treatment in any amount by assaying for any B/b, A/a, T/t VDR haplotype and furthermore, it does not teach the administration of any treatment in any amount. The specification teaches exhaustive examples serving to enable the increased risk of a human patient consuming at least 1302mg/day of calcium who were homozygous for the specific "baT" VDR genotype to myocardial infarction and arrythmias(8.31 and 3.63 times as likely respectively). The applicant's provide in Table 3, that heterozygotes for the VDR genotype, consuming at least 1302mg/day of calcium are 5.4 times more likely to experience myocardial infarction, and homozygotes consuming at least 1302mg/day of calcium are 8.31 times more likely to experience myocardial infarction as compared to those in the reference population. Furthermore, in Table 4, applicant's provide that heterozygotes for the VDR genotype, consuming at least 1302mg/day of calcium are 1.6 times more likely to experience myocardial arrythmias, and homozygotes consuming at least 1302mg/day of calcium are 3.63 times more likely to experience myocardial arrythmias as compared to those in the reference population.

The specification does not teach methods for predicting any patient's response to any treatment in any amount by assaying for any B/b, A/a, T/t VDR haplotype and furthermore, it does not teach the administration of any treatment in any amount. The specification lacks any teaching of the exact type(s) of treatment, amount(s) of treatment, protocol(s), genotype(s) of individual being tested, etc, as such information should be included in the specification so to teach anyone of skill in the art to make and use this method of prediction and administration. Much unpredictability exists in determining an association between the baT haplotype and the treatment of other type of heart diseases. The specification itself teaches that, "heart disease may include atrial or ventricular hypertrophy, aortic calcification and hypertension(Page 4), but omits any teachings of how the VDR genotype affects, or is associated with, these conditions. The specification merely speculates that the applicant's observations may "open the possibility that genotyping at the VDR gene locus might be of value in predicting the response to treatment with some of these drugs."(Pg 16 lines 27-28) The specification further reveals that "prospective clinical trials are needed to investigate the clinical and therapeutic implications of their results"(Pg. 17 lines 1-2). In tables 3 and 4, the increased chance of myocardial infarction and arrythmia(respectively) are shown in patients that have been administered at least 1302mg/day of calcium. The specification omits any other teaching that finds the VDR genotype to be of predictive value in the administration of any other compound and furthermore of the administration of calcium in any amount less than 1302mg/day. In addition, unpredictability exists in the specification's teaching of myocardial infarction's absent association with the VDR gene(Page 14). This lack of an association creates much unpredictability with respect to other heart diseases and their association to the VDR genotype. Furthermore, page 9 of the

specification postulates that the VDR haplotype may result in modification of calcium uptake, but provides no evidence to support this hypothesis. Therefore, it is further unpredictable as to how the haplotype would affect treatment with compounds other than calcium.

In addition to the lack of teachings in the specification, the art has reported findings that contribute to the overall unpredictability associated with Claims 17-19 of this invention. The exact role played by the polymorphisms in the VDR gene is uncertain. The art states that; "any influence of these polymorphisms on VDR transcription and/or its mRNA stability …is purely speculative(Carling et al, 1997). Carling et al. add that, "several components, thus, may balance the consequences of any influence of polymorphic VDR alleles…in vitro." As stated in *Vaek* (20 USPQ2d 1438), the specification must teach those of skill in the art how to make and how to use the invention as *broadly* as it is claimed" (emphasis added). The amount of guidance needed to enable the invention is related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher* 427 F. 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Predictability or lack thereof in the art refers to the ability of one of skill in the art to extrapolate the disclosed or known results to the invention that is claimed. If one of skill in the art can readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is unpredictability in the art. With respect to the present invention, the specification does not enable predicting the response of a subject to treatment, said method comprising analyzing genetic material of a subject to determine which of the B/b, A/a, or T/t allele(s) of the vitamin D receptor gene are present, in order to definitively determine the

underlying cause of the heart disease nor does it enable the administration of any treatment. The specification does not specify any examples of such well-established, *in–vitro* model systems or evidence in support for the ability of the VDR genotype to definitively predict, with any kind of treatment other than at least 1302mg/day of calcium, the response of a subject. Tables 3 and 4 have taught that less than 1302mg/day of calcium do not predictably confer an increased risk to myocardial infarction and arrythmia respectively as does doses of calcium totaling 1302mg/day or more. Therefore, the specification has not provided sufficient guidance as to how to select additional methods of prediction to different responses of different subjects to different treatments and furthermore to the administration of different treatments. As a result, neither the specification nor the art enable the prediction of any response of any subject to any treatment comprising analyzing any genetic material of any subject to determine which of any of the B/b, A/a, or T/t allele(s) of the vitamin D receptor gene are present, in order to definitively determine the underlying cause of the heart disease and to furthermore, to administer the appropriate treatment.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

A. Claims 17-19 are indefinite. Claim 17 is drawn to a method of predicting the response of a subject to treatment comprising analyzing genetic material of the VDR gene. However, the final process step is one of determining the underlying cause of the heart disease. Accordingly, it is unclear as to whether the claim is intended to be limited to methods of predicting the response of a subject to treatment comprising analyzing genetic material of the VDR gene or just for

determining the underlying cause of the heart disease as referred to in the preamble. Applicants should amend the claim to indicate how the step of predicting the response of a subject by analyzing the VDR gene results in the determination of the underlying cause of the heart disease.

B. Claims 18 and 19 are indefinite, as Claim 18 is multiply dependent on claim 17 and additionally refers back to the non-elected Claim 1. As a result, it is not clear to which method the claim refers. The claims should be amended to avoid a reference back to a non-elected claim and claims 18 and 19 should be amended to depend from only 1 claim.

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (703) 306-0284. The examiner can normally be reached on Monday-Thursday from 6:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W.Gary Jones, can be reached on (703)308-1152. The fax number for the Technology Center is (703)305-3014 or (703)305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (703)605-1237.

Sally Sakelaris
12/09/2002

CARLA J. MYERS
PRIMARY EXAMINER